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EXPERIMENTAL STUDIES ON THE NEUROGENIC HYPERTHERMIA

by

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INTRODUCTION

It is well known that neurogenic hyperthermia occurring shortly after a head injury and an intracranial operation is a serious prognostic sign.

Since the reports of Aronsohn & Sachs, Richet & Ott (1884) that the body temperature was raised by means of a caudate puncture, innumerable experimental and clinical studies have been made on the location of the temperature regulating center (Isenschmidt & Krehl, Keller, Bazett, Alpers & Erb, Ranson et al., Hess, Kurozu, Abé, McCrum, Sherwood, Massopust & Buchanan etc.). These observations indicate that the chief central mechanism controlling the body temperature is carried on the hypothalamus. Moreover, as to the exact location of the center or centers in the hypothalamus, the work of Ranson et al. has been generally accepted to be the most important.

They showed in the experiments by the aid of the Horsley-Clarke's stereotaxic instrument in the cat and monkey that the heat dissipation or loss "center" exists in the anterior hypothalamus (preoptic area) and the heat conservation or production "center" in the posterior hypothalamus.

In their experiments, the changes of the body temperature were observed under a certain, controlled high temperature or in an incubater regulated at 27 to 30°C during the first day or two or sometimes longer, and in a hot box (39～40°C) or in a cold box (−1.1～8.0°C) more several days after electrocoagulation for the examination of the ability to regulate against cold and hot.

Since hyperthermia in the man occurs under the usual environmental temperature, I investigated the mechanism of experimental neurogenic hyperthermia under the usual condition.

The experiments were performed to investigate the following two aspects.

(1) The changes of the body temperature after damaging the hypothalamus by the injection of chemicals or the electrocoagulation.

(2) The changes of the body temperature after primarily making a lesion in the hypothalamus and then secondarily giving stimulants intravenously or subarachnoidally.

I

1) Experimental Materials and Procedures for Measurement of the Body Temperature

The experiments were performed in one hundred and twenty adult healthy cats, which were above 1.5 kg in body weight and had been bred under a certain condition for at least several days before operation.

The body temperature was measured in rectum, inserting a clinical mercury thermometer about six centimeters deeply for over three minutes without binding the cats except at the operation under the usual room temperature of 10 to 28 degrees, centigrade.

2) Preliminary Experiments

1. The rectal temperature in normal cats:

The rectal temperature of an adult healthy cat averaged from data in 76 animals was found to be 39.0±0.1°C.

The lowest temperature recorded was 37.9°C and the highest 40.0°C.

	Experiment	Lowest-Highest	Mean Value & Err	Median Value	Standard Deviation
♂,	38	38.3－40.0°C	39.05±0.1°C	Md＝39.10°C	$\hat{\sigma}$＝0.66
♀,	38	37.9－39.6°C	38.87±0.1°C	Md＝38.85°C	$\hat{\sigma}$＝0.67

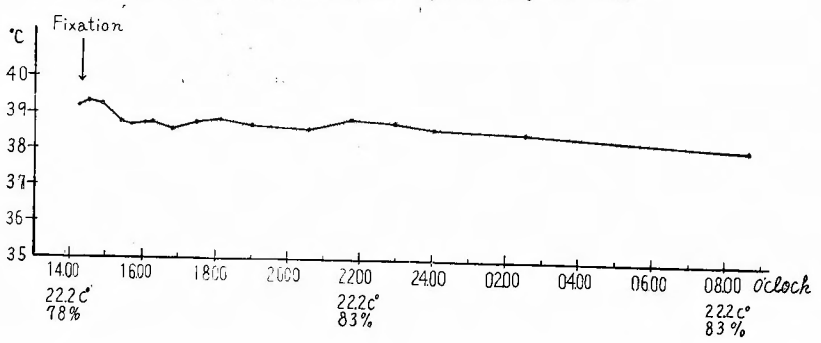
These readings show that there is a large individual variation in the rectal temperature. Therefore, in the present experiments, the rectal temperature 38 2 to 39.8°C was regarded as normal deviation.

2. Fixation of the animals:

A mature cat is fixed on a hammock in the prone position and the four limbs are allowed to hang down. Within 15 minutes immediately after fixation, the rectal temperature rose usually about 0.2 to 0.3°C. However, 30 minutes to 1 hour after fixation, it fell 0.5 to 1°C lower than that at the prefixation and continued so for 12 hours (Fig. 1).

These results are similar to those of Boehm & Hoffmann's experiments (1878).

Fig. 1 Change of the Rectal Temperature due to Fixation (Normal Cat).
♀ 2.1 kg Room temperature, 22.2 C, Humidity 78～83%



The fall of the rectal temperature after fixation in the cats seems to be similar as that in the man, monkey and rabbit.

3. Influence of fixation plus anaesthesia:

The rectal temperature generally falls in parallel with the depth of narcosis. Even with ether for 30 minutes it falls 1°C, and does not return to the preoperative value for at least three hours when kept in the fixating state (Fig. 2).

4. Craniotomy (Trepanation).

The rectal temperature falls also according to the magnitude of operative procedures and when kept in the fixating state, the recovery is very slow (Fig. 3), while if the animal is made freely movable immediately after operation, the temperature returns steadily to the preoperative level (Fig. 4).

It takes usually about one hour to finish all procedures such as fixation, narcosis and trepanation, and the rectal temperature becomes the lowest 20 to 30 minutes after relieving from fixation, and usually 2.5 to 3.0°C lower than the preoperative value. Then one to two hours later it returns considerably rapidly (up to the level 1 °C lower than at preoperation), and thereafter slowly to the preoperative rectal temperature in the following 7 to 9 hours (about 10 hours after operation), but usually does not rise higher above the prior temperature.

Fig. 2. Influences of Fixation plus Ether Anaesthesia on the Body Temperature.
♀2 2.1kg 23°C, 79%

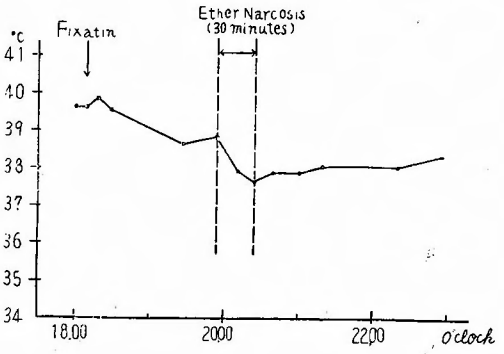


Fig. 3 Influence of Craniotomy (Mere Trepanation). Fixation Continuing after Operation.
♀12 2.9kg 25~26°C 80~94% ♀13 2.6kg 24~26°C 75~84%

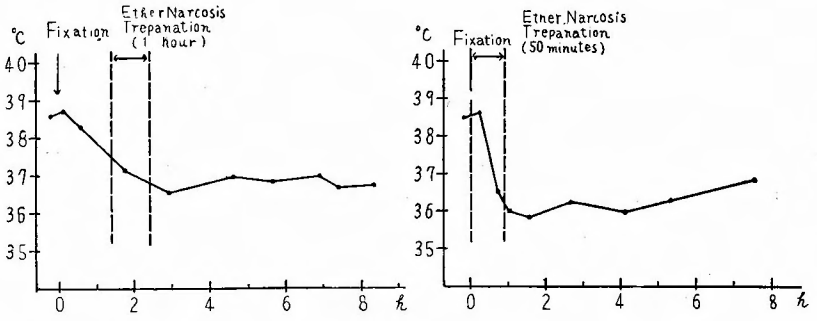
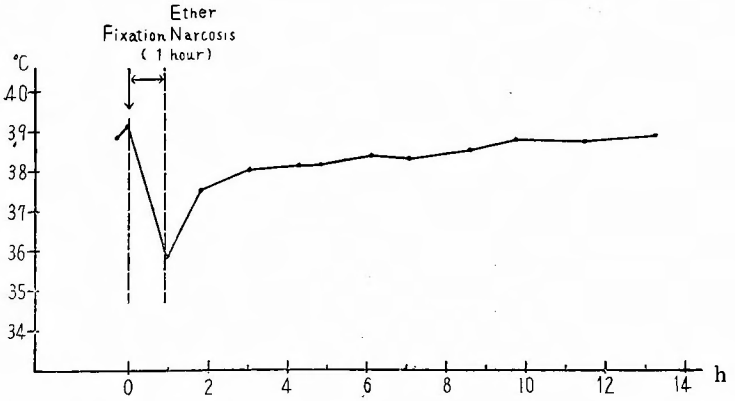


Fig. 4 Influence of Craniotomy (Mere Trepanation). Relieved from Fixation Immediately after Operation.
♀79 2.9kg 13.5~16.0°C 54~80%



5. Limitations of hyperthermia in the cat:

In order to know how much the rectal temperature may be raised under the

usual environmental temperature and in the free state, either typhoid vaccine (10 mg/1.0cc) or compound vaccine consisting of typhoid and paratyphoid A, B (Pharmacopoeia Japonica) was injected intravenously or intramuscularly. Even with this method, the rectal temperature did not rise more than 41°C; within 12 hours after intravenous injection of typhoid vaccine, 2.0 cc per kilogram body weight, average value of the highest rectal temperature in four cases was 39.68°C and the highest rising degree 0.97°C, and with 6.0 cc per kilogram body weight 40.65°C and 1.15°C respectively, while five hours after intravenous injection of 2.3 cc of the compound typhoid vaccine per kilogram body weight, the temperature rose to 40.05°C and the rising degree was 1.5°C, and with 3.5 cc per kilogram body weight 40.35°C and 1.5°C respectively.

In case of intramuscular injection the beginning of fever was delayed and the rising degree lowered than in case of intravenous injection.

3) Criteria for the Fever Reactions in the Present Study.

As above mentioned, even with typhoid vaccine, there is a limitation of hyperthermia in the cat and the fixation, narcosis and operative procedures suppress the fever rising as well as the recovery of the rectal temperature under the usual condition. Thus in the present study, all procedures including the fixation, narcosis, trepanation and an intracranial operation were finished as rapidly as possible, usually within one hour. Then the animals were left freely movable and the rectal temperature was measured in the free state. In the present experiment, therefore, as the criteria for the fever reactions, the rising degree of the rectal temperature during 12 hours atfer operation was taken into consideration, and the following four types were devided according to the rising degree.

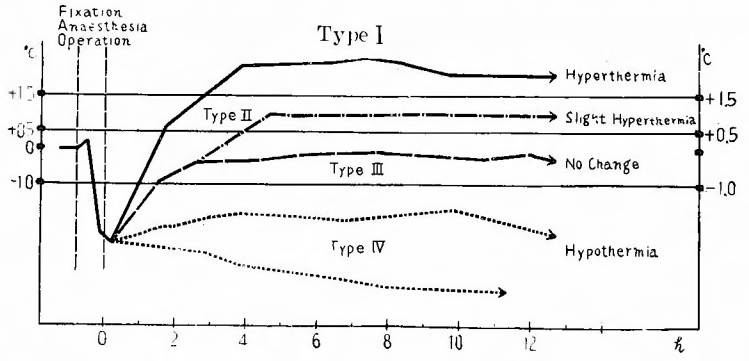
Type 1 belongs to "hyperthermia" in which the rising degree is over 1.5°C and continues for at least 3 hours.

In type 2, so-called "slight hyperthermia", the rising degree is 0.5 to 1.5°C and continues for at least 3 hours.

In type 3, so-called "no change", the rising degree is from minus 1.0°C to plus 0.5°C.

In type 4, "hypothermia", the rise in the rectal temperature is under minus 1.0°C (Fig. 5).

Fig. 5 Criteria for the Fever Reactions in the Present Studies.



II

(I) Fever experiments by primary single procedure.
1. Intracerebral injection of pure nicotine
2. Intracerebral injection of various chemicals
3. Intracerebral electrocoagulation

(II) Fever experiments by compound stimulation

(III) Fever experiments by delayed secondary arachnoid stimulation

EXPERIMENTAL METHODS

The HORSLEY-CLARKE's stereotaxic instrument was used. Anesthesia was induced only lightly by ether, so that the animal was nearly awakened at the end of the operation. Care was taken to keep all techniques aseptic, injecting with procaine-penicillin 15×10^4 unit into the back muscles after operation.

The experimental brains were examined microscopically to determine the exact situation and extent of the lesions.

The specimens were sectioned serially at 30μ in thickness after dehydrating in alcohol during 2 weeks and celloidin embedding.

Every 3rd section was stained with thionine (NISSL's stain) for cellular study, its adjacent section by YASHIRO's modified method of WEIGERT's myelin stain with EHRLICH's hematoxylin for fibers and with hematoxylin-eosin for other findings.

The hypothalamus was divided into four parts; the anterior, superior, middle and posterior regions.

1. The anterior region includes ganglion basale opticum and preoptic area.
2. In the superior region nucl. hypothalamus parvocellularis et dorsalis, nucl. infundibularis posterior, the anterior part of Vicq d'Azyr and upper subthalamus [upwards from nucl. filiformis (paraventricularis)] were included.
3. The middle region includes tuber cinereum, nucl. hypothalamus medialis et lateralis, nucl. infundibularis anterior et medialis, anterior part of columna fornicis descendens.
4. The posterior region includes corpus mammillare as the center and its adjacent area.

The size of a lesion was described with the following signs; Small lesion (+) which is similar in size as the width of the puncture canal (about 0.5mm).

Middle lesion (++) presenting dimensions of one to two mm.

Large lesion (+++) presenting dimensions of more than these.

EXPERIMENTAL RESULTS

(I) Fever experiments by primary single procedure

1. Intracerebral injection of pure nicotine

Since nicotine is a strong stimulant and at the same time a destructive agent, nicotine was injected into the hypothalamus in which the regulation center of the body temperature has been accepted to exist.

A syringe-needle, 1/4 mm in size, 13 cm in length, was connected with the HORSLEY-CLARKE's stereotaxic instrument and inserted into the hypothalamus on one or both sides.

Table 1. Intracerebral Injection with Pure Nicotine

Cat Case	Type	R. Hypothalamus Anterior	R. Hypothalamus Superior	R. Hypothalamus Middle	R. Hypothalamus Posterior	R. Other Parts	L. Hypothalamus Anterior	L. Hypothalamus Superior	L. Hypothalamus Middle	L. Hypothalamus Posterior	L. Other Parts
♂23-1	I										Nucleus caudatus ++
♂23-2	II		+			Thalamus ++					(Nucleus caudatus ++)
♀17-2	〃					Thalamus ++					Thalamus ++)
♂5	〃	+	++	++				+	++		
♀27-2	〃	(++)					++				
♀27-1	III	++									
♀17-1	〃										Thalamus ++
♂6	〃				++				++		
♀21	〃		+	+							Thalamus ++
♀13	IV						+		+		Capsula interna +
♀16	〃										Thalamus ++
♀18	〃		++	++				+	+		
♀14	〃										Capsula interna +

Size of Lesion: small + middle ++ large +++
Sign in parenthesis ( ) indicates the size of the lesion made by the previous operation.

Then 0.01 cc of nicotine (produced by Dr. THEODOR SCHUCHARDT) was injected.

Results (Table 1):

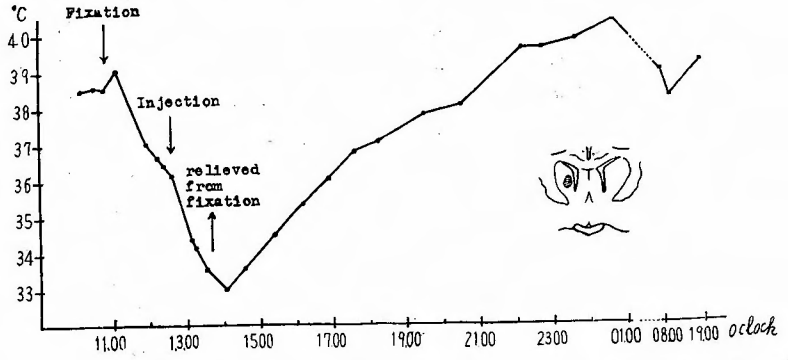
Nine cases among twenty-two died either immediately or during twelve hours after injection.

Survival cats were six in the one-side-injection group and seven in the both-side-injection group. Out of 13 cases which survived, six had not lesions in the hypothalamus, but in the nucleus caudatus or thalamus. Since the overdosis of nicotine was employed in this experiment, a serious intoxication resulted, so that in any case, even if the animal did not die, shock syndrome such as hypothermia and consumption appeared and prevented a rise in the body temperature after injection. Even in one case (♂ 23) which showed hyperthermia type I, such a shock reaction is evidenced, as shown in the fever curve in Figure 6.

Now the mechanism of the shock reaction of nicotine was analyzed.

Under Ouropan soda (methylhexabitalum soluble, Shionogi, Japan) anesthesia, the blood pressure was measured directly by inserting a cannula into the femoral artery. Then 0.01 cc of pure nicotine was injected into the abdominal hypoderm, frontal cortex or the hypothalamus. In any

Fig. 6 Unilateral Injection with Pure Nicotine into Left Caudate Nucleus.
♂23 3.7kg 14.5~20°C 69~86%



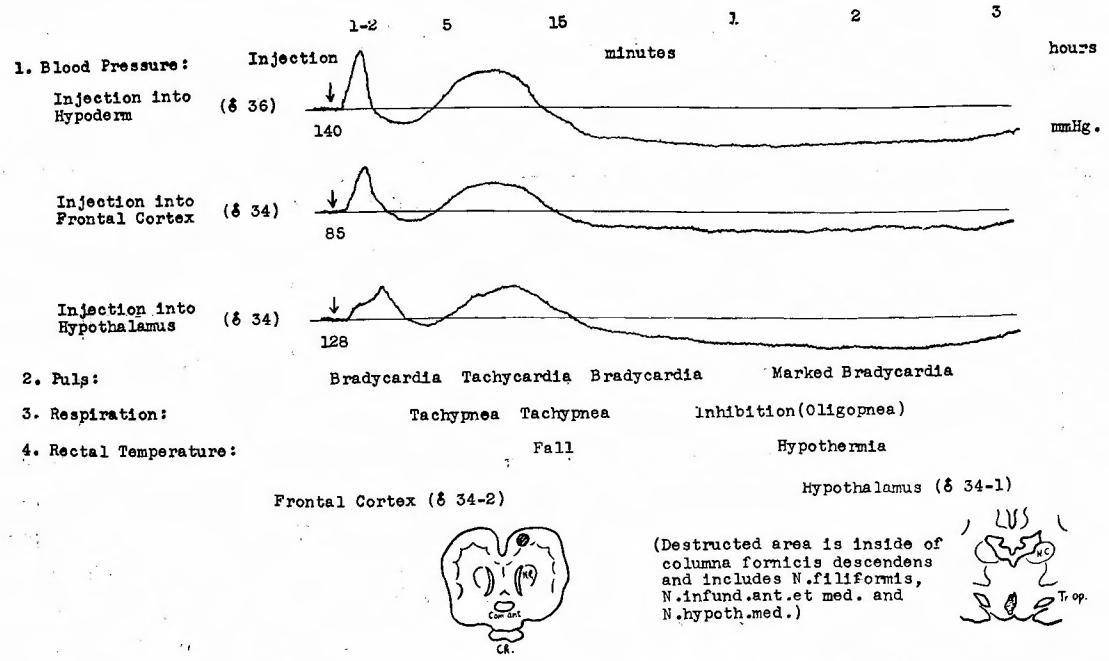
The sketch representing a frontal section at the level of the optic chiasm

case, the blood pressure increased sharply within one to two minutes, followed by a transitional fall, then slowly increased in five to fifteen minutes after injection and showed hereafter a continuous fall. The puls is usually bradycardic, the respiration is frequent at the beginning and then inhibited. The rectal temperature remains low for more than several hours.

These reactions, especially in the blood pressure, were almost the same regardless the part injected, only different in the degree and the time of occurrence of the response, according to the concentration and quantity of nicotine (Fig. 7).

Accordingly, pure nicotine may be considered to be unsuitable for our fever experiment because of its severe general effect after absorption.

Fig. 7 Nicotine shock



The cross-hatched area indicates the site of the injection.

Table 2. Intracerebral Injecti on with Various Chemicals

Cat Case	Type	R. Hypothalamus Anterior	R. Hypothalamus Superior	R. Hypothalamus Middle	R. Hypothalamus Posterior	R. Other Parts	L. Hypothalamus Anterior Superior	L. Hypothalamus Middle	L. Hypothalamus Posterior	L. Other Parts
♂88 T.	I						+			
♀70 S.	〃		++				++			
♀60 S.	〃		+	(+)			+			
♀16-1N.	II			++				+		
♀48 N.	〃	+++				Thalamus ++, Caudate Nucleus ++	+++			Thalamus ++, Caudate Nucleus ++
♀73 S.	〃	++		+			++	+	(+)	
♀50 S.	〃	++		(++)				(+)		
♀46-2N.	〃	++				Thalamus + Thalamus ++				Thalamus + Thalamus ++
♂28 L.	III				++				++	
♂42 N.	〃									
♀49 N.	〃									
♂43 N.	IV	++					+			
♂44 N.	〃	++	+							

N. ♂ 43, 44.: 0.1% Nicotine in 40% Glycerine 0.01cc. T. ♂ 88. : Typhoid Vaccine (10mg/cc) 0.1 cc.
♂ 42, 46.: 0.1% Nicotine in 40% Glucose 0.01cc. S. ♀ 50. : 0.1% Sublimate 0.01cc.
♀ 48. : 2.0% Nicotine in 10% Arabic gum 0.01cc. ♀ 60. : 0.1% Sublimate 0.02cc.
♀ 49. : 2.0% Nicotine in Glycerine 0.01cc. ♀ 70, 73. : 0.1% Sublimate 0.05cc.
L. ♂ 28. : Langecaine (Procaine et al.) 0.01cc.

2. Intracerebral injection of various chemicals

Nicotine diluted with glycerine, glucose or with arabic gum was employed for the purpose of reducing a serious reaction of pure nicotine and producing the focal stimulation or destruction in the brain. Sublimate which has mainly a destructive effect, Langecaine (procaine etc., Kaken, Japan) which has a long lasting anesthetic effect or typhoid vaccine were also employed.

The details of the data obtained from these experiments are presented in Table 2. The rising degree was higher than in cases of the preceding experiment with pure nicotine.

3. Intracerebral electrocoagulation

Electrocoagulation was performed, using high frequency current (60-70 V, 30-45 mA, 5-10 seconds) or direct current (6 V, 30 seconds -1 minute or 20-30 V, 5 seconds) in few cases, with monopolar or bipolar electrode made of card clothing steel wire of 12 mils (0.3 mm) diameter and

applied an insulation paint for high frequency and white lacquer.

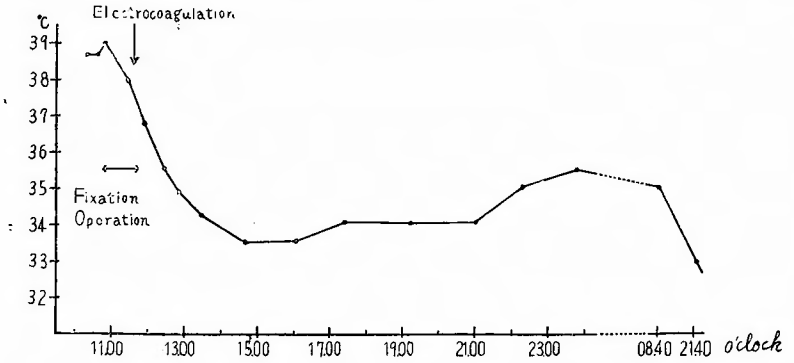
Results (Table 3) :

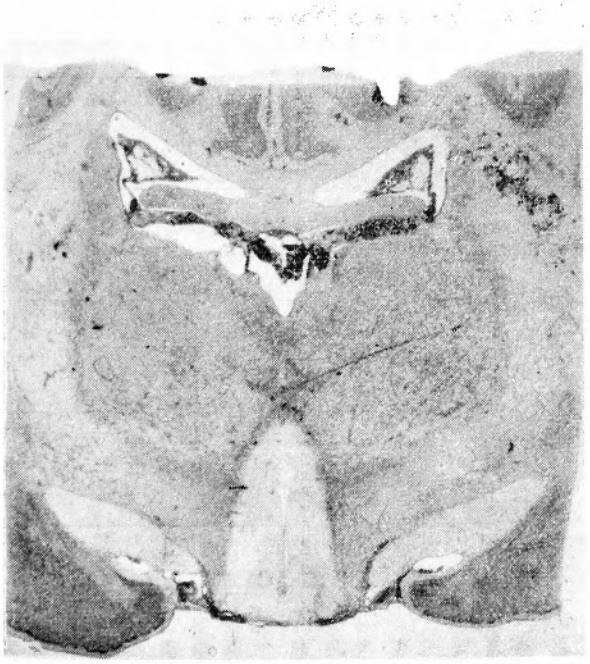
Out of forty-eight cases in this experiment, the sites of electrocoagulation were bilateral hypothalamus in 23 cases, unilateral hypothalamus in 10 cases, in and around mesencephalic central grey in 11 cases and other regions in 4 cases (items; each one case, head part of caudate nucleus, thalamus, parietal subcortex or in and around chorioidea respectively).

In the cases in which remarkably high body temperature was caused, panting was observed, but never shivering.

Generally speaking, the rectal temperature seems to be more easily raised in cases in which a moderately large lesion, not enough to produce shock syndrome,

Fig. 8 Massive Electrocoagulation in the Hypothalamus.
♂86 4.2kg 10~13°C, 59~95%.





Photomicrograph 1. (Thionine stain) representing a frontal section of the diencephalon of cat ♂ 86.

was found in the hypothalamus, than in cases with a smaller lesion. If a lesion is large and involves almost all areas of the hypothalamus, the animal reveals hypothermia and dies unless proper treatment is given (Fig. 8, Photomicrograph 1).

It is difficult to make a comparison fairly of fever reaction between cases with anterior hypothalamic lesion and cases with posterior lesion, for in this experiment, there were no cases in which a lesion was made exclusively in the posterior hypothalamus. However, in cases in which hyperthermia type I was observed, the lesions were found either in the anterior or middle region of the hypothalamus

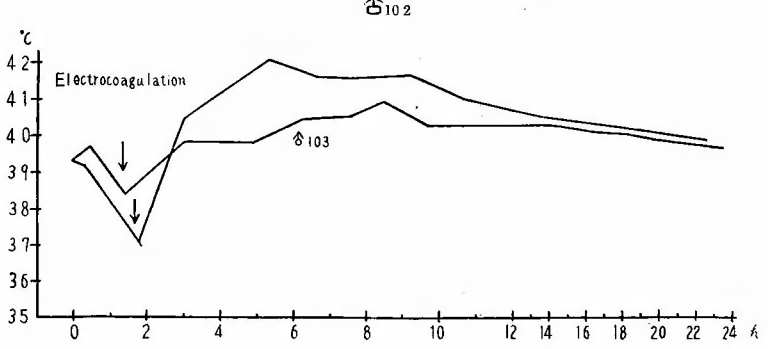
Table 3. Intracerebral Electrocoagulation

Cat Case	Type	R.					L.					In and Around Central Grey
		Hypothalamus				Other Parts	Hypothalamus				Other Parts	
		Anterior	Superior	Middle	Posterior		Anterior	Superior	Middle	Posterior		
♂ 102	I	±±	+	±±			±	+	±			
♂ 103	〃	±	+	±			±±	+	±±			
♂ 67	〃	±		±			±		±			
♀ 92	〃	+		±			+		±			
♀ 95	〃						±		±			
♂ 104-2	〃					(Chorioidea ±)					Chorioidea ±)	±
♂ 66	II	±					±					
♂ 26	〃	+		+	+		+		+	+		
♀ 65	〃	+		+			±		+			
♂ 74	〃			±				±	±			
♀ 82	〃						±±	±				
♀ 83-1	〃						±					
♂ 94-1	〃	±										±
♂ 90	〃											±±
♀ 105	〃											±±
♂ 84	〃											±±
♀ 91	〃											±±
♀ 77	〃											±±
♂ 80-2	〃						(±)		(±±)			+
♂ 76-2	〃	(+)					(+)					
♂ 53-2	〃		(+)	(+)	+				(+)	+	(Caudate Nucleus +)	
♀ 83-2	〃	±					(±)					
♂ 69	III	+		±			±		±±			
♀ 71	〃	±±					±±					
♀ 63	〃	±					±±					
♂ 76-1	〃	+					+					
♀ 22	〃			+					+			
♂ 94-2	〃	±±		+								

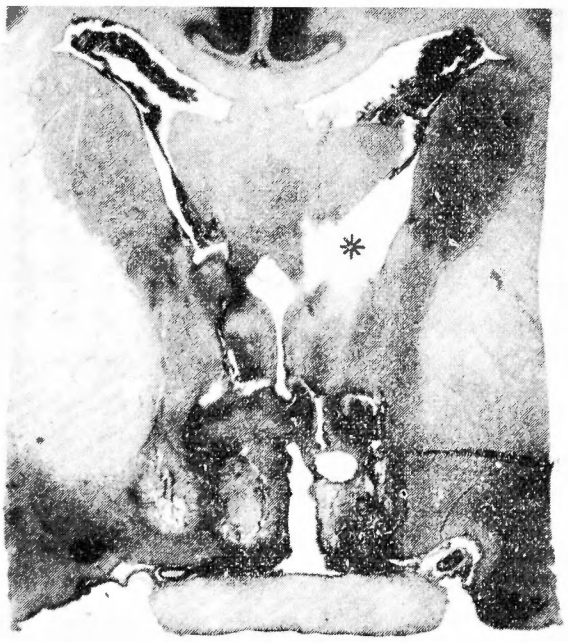
♂ 80-1	Ⅲ						++		+++			
♂ 97-1	〃						++					
♂ 104-1	〃					Chorioidea ++					Chorioidea ++	
♂ 106	〃					Subcortex +++						
♀ 108	〃										Thalamus +++	
♀ 30	〃										Caudate Nucleus ++	
♂ 89	〃											++
♂ 97-3	〃	(++)	(+)	(+)			(++)					++
♂ 88-3	〃	(++)	(+)	(+)			(+)					++
♂ 97-2	〃	++	+	+			(++)					
♂ 86	Ⅳ	++	++	+++	+++		++	++	+++	+++		
♀ 109	〃		+	+++	++			+	+++	++		
♀ 110	〃		+	++	+++			+	++	+++		
♀ 93	〃	++	+				+++	+++	+++	+++		
♀ 45	〃			++	++		+++		++	++		
♀ 79	〃	++										
♀ 99	〃	+++										
♂ 96	〃	++										
♀ 50-2	〃	(+)	+	+	++		(+)		+	++		
♂ 88-2	〃	++	+	+			(+)					

Fig. 9 Bilateral Electrocoagulation in the Anterior Hypothalamus.

♂102 3.75 kg 26.1～26.7℃ 53～66% ♂103 3.3 kg 21.1～26.1℃ 〃 66～76.5%



Photomicrograph 2. (Thionine stain) representing a frontal section of the diencephalon of cat 숫 102.



Photomicrograph 3 (Thionine stain) representing a frontal section of the diencephalon of cat 숫 103.
* artificial defect at the time of section.

and not in the posterior.

This result seems to indicate that hyperthermia is apt to be resulted when the anterior hypothalamus is electrocoagulated. In No. 102 (숫) and No. 103 (숫) which showed a remarkable rise in the body temperature, the region from the middle to the anterior hypothalamus was destroyed bilaterally, the posterior hypothalamus being intact (Fig. 9, Photomicrograph 2, 3).

However from the results above mentioned, it would be difficult to draw a definite conclusion as to the relation between the location of the lesions and the fever reaction because of some discrepancies in the data. The difference of fever reaction between symmetrization and asymmetrization of bilateral lesions was scarcely noticed, and that between uni- and bilateral electrocoagulation likewise was not so remarkable (Fig. 10, 11, 12. Photomicrograph 4).

Therefore, the effect of electrocoagulation is regarded as not solely destructive but as stimulative for sometime after operation, because for the explanation of the above facts it would be reasonable to assume the abnormal excitation widely spreading from the site of a lesion and involving bilaterally wide areas of the hypothalamus.

The lesion in and around the mesencephalic central grey was relatively easy to raise the body temperature by electrocoagulation similarly as the lesion in the hypothalamus.

Results of the fever experiments

Fig. 10 Unilateral Electrocoagulation in the Hypotalamus.
♀95 2.5kg 12.7~14.7℃, 75.5~83%

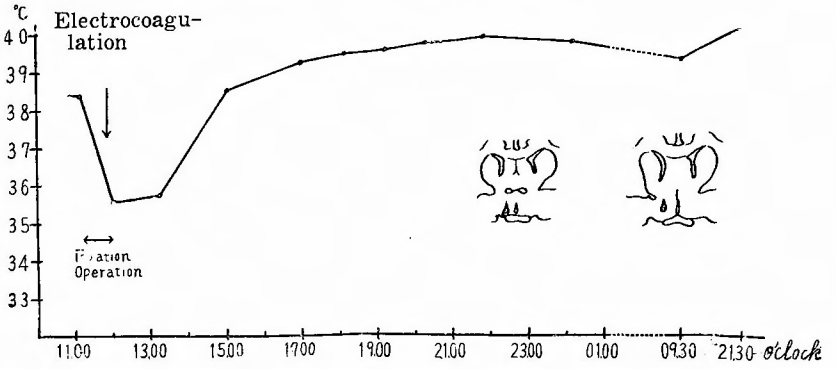


Fig. 11 Secondary Unilateral Electrocoagulation after the Previous Electrocoagulation on the Other Side.
♀83 3.3kg 11.6~13.0℃, 65~78%

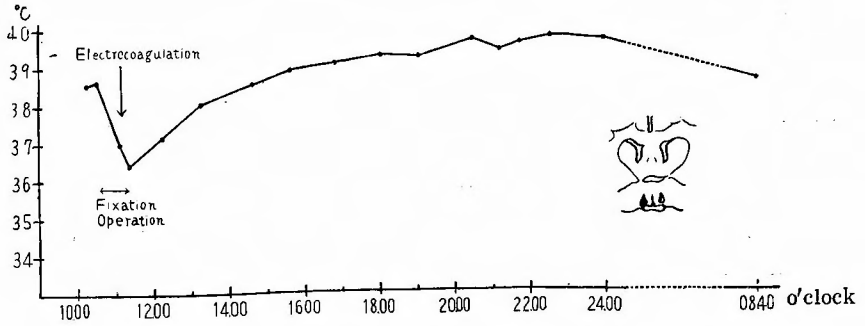
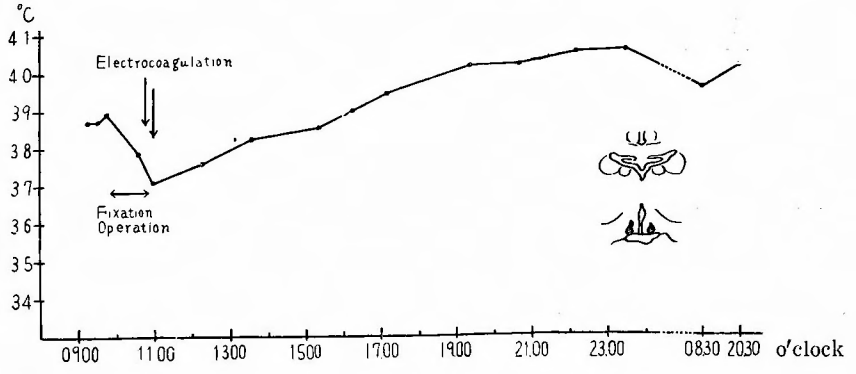


Fig. 12 Bilateral Electrocoagulation in the Hypothalamus.
♂67 3.8kg 22.5~23.6℃, 76.5~83%



by primary single stimulation are arranged according to the pyrogenic procedure and the localisation of damage, and presented en bloc in Table 4, 5. Differences in reaction by different procedures and localisations are not definite, but merely relative.

Type I hyperthermia in this series of experiments under the usual room temperature was seen in one case with the pure nicotine injection, in three with injections of various chemicals, and in six with the electrocoagulation, but the animal which showed over 2.0°C in rising degree and above 41°C hyperthermia

Table 4. Primary Fever Experiments Arranged According to the Methods of Pyrogenesis.

Type	Electrocoagulation			Various chemicals injection	Pure nicotine injection
	Bilateral		Unilateral		
Ⅰ	5(1)	6(1)	1	3	1(1)
Ⅱ	13(7)	16(7)	3	6(1)	4(2)
Ⅲ	10(4)	16(7)	6(3)	2(1)	4(2)
Ⅳ	7	10	3	2	4(1)
Total	35(12)	48(15)	13(3)	13(2)	13(6)
Within 12 hours after operation	Electrocoagulation			Various chemicals injection	Pure nicotine injection
	Bilateral		Unilateral		
Highest temperature above 41℃	1	1	0	0	0
Highest rising degree over 2.0℃	1	1	0	0	0

Number in parenthesis indicates the number of cases stimulated in the area other than the hypothalamus.

Table 5. Primary Fever Experiments Arranged According to the Localisations of the Damage.

Type	Hypothalamus (total cases)	Hypothalamus (except cases with pure nicotine injection)	Other parts	In and around central grey
Ⅰ	8	7	1	1
Ⅱ	16	14	3	7
Ⅲ	12	12	8	3
Ⅳ	15	12	0	0
Total	51	45	12	11
Within 12 hours after operation	Hypothalamus (total cases)	Hypothalamus (except cases with pure nicotine injection)	Other parts	In and around central grey
Highest temperature above 41℃	1	1	0	0
Highest rising degree over 2.0℃	1	1	0	0

was solely one with the electrocoagulation.

(II) Fever experiments by compound stimulation

In the above mentioned fever experiments, it was realized that hyperthermia was not easily produced by a single primary procedure in and around the hypothalamus.

Accordingly in the next experiment, a lesion was made in the hypothalamus preliminarily and then one or two additional pyrogenic procedures were done simultaneously or successively; e. g. cisternal puncture, suboccipital injection with air or typhoid vaccine, subarachnoidal infusion with physiological salt water, intravenous

injection with typhoid vaccine or physiological salt water, intracerebral (frontal lobe) injection with typhoid vaccine, puncture in the hypothalamus, intrahypothalamic injection with typhoid vaccine, electrostimulation of the hypothalamus and intracranial insertion of a laminaria piece etc.

Results (Table 6) :

There were thirteen cases in all including six cases injected with typhoid vaccine. Body temperature rising was brought about more easily in this experiment

Table 6. Compound Stimulation

♀, ♂: Case injected with typhoid vaccine

Type	Successive stimulation following hypothalamic electrocoagulation		Compound stimulation some days after hypothalamic damage or mere trepanation		Total
I	♂87	1	우22, ♂42, ♀49, ♂76, 우79.	5	6
II	♂84	1	우48, ♂53, 우65-1, 우65-2, 송76.	5	6
III		0		0	0
IV	우75	1		0	1
Total		3		10	13

Within 12 hours after operation	Successive stimulation following hypothalamic electrocoagulation	Compound stimulation some days after hypothalamic damage or mere trepanation	Total
Highest temperature above 41℃	0	0	0
Highest rising degree over 2.0℃	0	우22, ♂76. 2	2

우22 Electrostimulation in posterior hypothalamus + Injection with physiological salt water into liquor space (after electrocoagulatlon in anterior hypothalamus)

우48 Puncture in posterior hypothalamus (after injection with nicotine-arabic gum in anterior hypothalamus)

우65-1 Laminaria piece insertion in frontal lobe (after insertion of a piece of gelatine sponge in aquaeductus mesencephali + Electrocoagulation of anterior hypothalamus)

우65-2 Laminaria piece insertion in frontal lobe on the other side (after the same procedure as in the above case)

우75 Electrocoagulation in anterior hypothalamus + Cisternal injection with air

송76 Cisternal injection with air + Intravenous injection with physiological salt water (after electrocoagulation in anterior hypothalamus)

우79 Cisternal injection with air + Intravenous injection with physiological salt water (after mere trepanation)

Cases injected with typhoid vaccine

♂42 Injection with typhoid vaccine into frontal cortex (after mere trepanation)

♀49 Injection with typhoid vaccine into frontal lobe (after injection with nicotine-arabic gum in anterior hypothalamus)

♂53 Injection with typhoid vaccine into frontal lobe (after electrocoagulation in anterior hypothalamus)

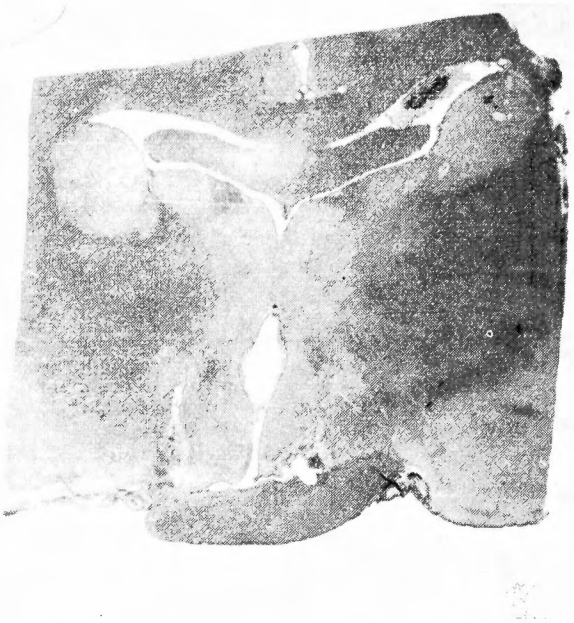
♂76 Cisternal injection with typhoid vaccine and air (after electrocoagulation in anterior hypothalamus and in and around aquaeductus mesencephali)

♂84 Electrocoagulation in posterior hypothalamus + Cisternal puncture + Intravenous injection with typhoid vaccine

♂87 Electrocoagulation in posterior hypothalamus + Injection with typhoid vaccine into hypothalamus

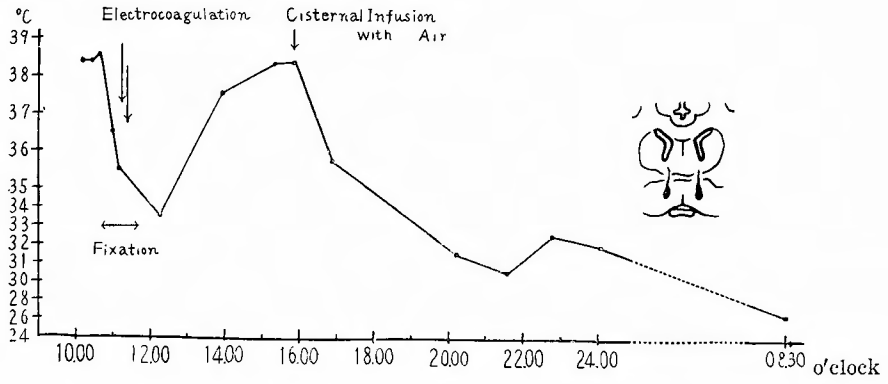
than in the previous experiment. But because stimulating or destructive effects are apt to be excessive, if two or more heavy procedures are done at the same time, the animals occasionally fell into the shock state rather than produced the high body temperature (Figure 13). Thus the rising degree of the body temperature in case of secondary successive stimulation some days after the previous damage was higher than in case of simultanous compound procedures. With or without use of typhoid vaccine, there were no cases of above 41°C hyperthermia, but 2 cases above 2°C of rising degree.

(III) Fever experiments by delayed secondary arachnoid stimulation



Photomicrograph 4. (Hematoxylin-eosin stain) representing a frontal section of the diencephalon of cat 古 67.

Fig. 13 Bilateral Electrocoagulation in Preoptic Area and Cisternal Infusion with Air.
♀75 1.6kg ♂ 12.2～13°C, 72～78%



——Influence of arachnoid stimulation upon the rectal temperature in the cat having fully recovered from destructed lesions in the hypothalamus——

Arachnoid stimulations were secondarily given to the animals with destructive lesions in the hypothalamus, after an interval long enough to recover their constitutional reserve powers.

Stimulation methods were shown in Table 7.

The experiment was done from two days to three months after destruction in various parts of the hypothalamus.

Table 7. Stimulation Methods

Infusion Route	Infusion Material	Infusion Amount
Cisterna magna	Typhoid vaccine	1.5 cc
	Physiological salt water	1.5 cc
	Ringer's solution	1.5 cc
	Air	4.0–6.0 cc after pumping out liquor 2.0 cc
Parietal subarachnoid space	Typhoid vaccine	1.5 cc
	Physiological salt water	1.5 cc
Vein	Typhoid vaccine	2.0 or 6.0 cc per kg body weight

Injections into the space of cerebrospinal fluid were done by the following two ways; (i) through a trephine hole into the parietal subarachnoid space with a needle one quarter mm in size and (ii) through suboccipital puncture with a half mm size needle.

Injection volume was 1.5 cc in all cases.

Physiological salt water and RINGER'S solution were applied after being warmed to the body temperature, but typhoid vaccine was not warmed. Air infusion by cisternal puncture was done by pumping in from 4 0 to 6.0 cc of air immediately

Table 8. Secondary Experiments (1)

Typhoid Vaccine Injection

Injection route	Previous procedures	Size of lesion	Cat	Within 12 hours after injection	
				Highest rising degree(℃)	Highest rectal temperature(℃)
Cisterna magna (1.5 cc)	no operation		♀59	1.15	40.75
	damage bilateral in anterior hypothalamus	+	♂53	1.7	41.2
		+	♀60	1.5	40.3
Subarachnoid space (1.5 cc)	mere trepanation		♀63	1.2	40.65
	damage bilateral in anterior hypothalamus	+	♀60	1.75	41.05
		+	♂53	1.5	41.1
Vein (2.0 cc per kilogram body weight)	no operation		♂88	1.12	39.42
			♂87	1.0	39.9
			♀50	0.9	39.65
			♀40	0.75	39.75
	mere trepanation		♂58	1.55	40.0
	damage bilateral in anterior hypothalamus	+	♀60	1.9	41.45
		++	♀65	1.85	40.7
		+-	♂53	1.55	40.45
	damage bilateral in anterior and posterior hypothalamus	++	♀46	1.8	40.6
Vein (6.0 cc per kilogram body weight)	no operation		♀61	1.15	40.65
	damage bilateral in anterior hypothalamus	+	♂53	1.8	41.25

Table 8. Secondary Experiments (2)

Air Infusion

Infusion route	Previous procedures	Size of lesion	Cat	Within 12 hours after injection	
				Highest rising degree(℃)	Highest rectal temperature(℃)
Cisterna magna (inject 4.0–6.0 cc of air after pumped out 2.0 cc of liquor)	no operation		♂106	1.75	40.15
			♂109	1.66	40.3
	mere trepanation		♀63	1.05	39.35
	damage bilateral in anterior hypothalamus	++	♂66	1.55	41.35
		+++	♂69	1.37	40.0
		++	♀83	1.11	39.6
		+++	♂67	0.95	40.25
		+++	♂103	0.8	40.6
		++	♀92	0.8	40.4
		+++	♀71	0.75	39.45
	damage bilateral in anterior and posterior hypothalamus	+	♂53	2.55	41.15
		+	♀60	1.4	40.1
	damage on one side of anterior hypothalamus	++	♀95	1.2	39.6
		++	♂94	0.94	39.5
	damage on one side of thalamus	+++	♀108	1.43	40.24

Ringer's Solution Infusion

Infusion route	Previous procedures	Size of lesion	Cat	Within 12 hours after infusion	
				Highest rising degree (℃)	Highest rectal temperature(℃)
Cisterna magna (inject 1.5 cc of Ringer's solution)	damage on one side of anterior hypothalamus	++	♂94	1.05	40.15
		++	♂96	0.8	40.2

after pumping out 2 0 cc of cerebrospinal fluid of watery clearness. Intravenous injection was performed from the femoral vein at the back fixation.

Merely during the air injection was used slight ether anaesthesia in all.

Other experimental procedures were the same as in the previous experiments.

Results (Table 8, 9):

Table 8 shows the highest rectal temperature and the highest rising degree which were revealed respectively within twelve hours after injection. Table 9 shows collectively the fever types in the cases preliminarily having destructive lesions in the hypothalamus as compared with the control cases with no intracranial operation but mere trepanation.

The differences in fever reaction according to the localisation or to the bilateral symmetry of destructive lesions were not so remarkable.

Hypothermia (shock) was not observed in the present experiment except in the cases in which the brain injury and bleeding took place due to the awkward technic of injection. Fever rising reaction was more remarkably noted in the cases which had multiple small and bilateral lesions in the hypothalamus than in those with a large but merely unilateral lesion. The reaction was also more marked in the cases

Table 8. Secondary Experiments (3)

Physiological Saltwater Infusion

Infusion route	Previous procedures	Size of lesion	Cat	Within 12 hours after injection	
				Highest rising degree(℃)	Highest rectal temperature(℃)
Cisterna magna (1.5 cc)	no operation		우52	0.4	39.2
			송68	0.25	39.45
	mere trepanation		송58	1.04	39.74
	damage bilateral in anterior hypothalamus	+	우60	2.1	41.2
		++	우83	1.3	39.55
		+	송53	1.25	39.65
		++	우92	0.75	40.65
		++	송67	0.7	38.95
		+++	우71	0.6	39.65
		++	우73	0.5	39.04
	damage bilateral in anterior and posterior hypothalamus	+	송54	2.1	40.9
	damage unilateral in anterior hypothalamus	++	우95	1.82	40.2
		+++	송94	1.35	39.65
Subarachnoid space (1.5 cc)	mere trepanation		우58	0.4	39.35
	damage bilateral in anterior hypothalamus	+	송53	0.57	40.0
	damage bilateral in anterior and posterior hypothalamus	+	송26	1.9	40.1
		+	우61	1.7	40.4
		+	송54	1.6	41.1

Table 9. Secondary Experiments in Animals

Having Previous Hypothalamic Lesion (36 cases)

Infusion route / Type	Cisterna magna				Subarachnoid space		Vein	Total
	Typhoid vaccine	Physiological salt water	Ringer's solution	Air	Typhoid vaccine	Physiological salt water	Typhoid vaccine	
I	2	3	0	2	2	3	5	17
II	0	7	2	9	0	1	0	19
III	0	0	0	0	0	0	0	0
IV	0	0	0	0	0	0	0	0
Total	2	10	2	11	2	4	5	36

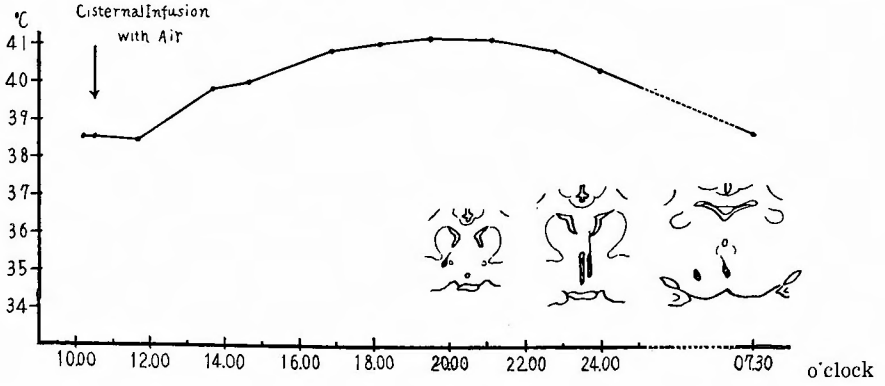
Within 12 hours after infusion	Cisterna magna				Subarachnoid space		Vein	Total
	T.	P.	R.	A.	T.	P.	T.	
Highest temperature above 41℃	1	1	0	2	2	1	2	9
Highest rising degree over 2.0℃	0	2	0	1	0	0	0	3

Previously no operation or mere trepanation (15 cases)

Type \ Infusion route	Cisterna magna				Subarachnoid space		Vein	Total
	Typhoid vaccine	Physiological salt water	Ringer's solution	Air	Typhoid vaccine	Physiological salt water	Typhoid vaccine	
I	0	0		2	0	0	1	3
II	1	1		1	1	0	5	9
III	0	2		0	0	1	0	3
IV	0	0		0	0	0	0	0
Total	1	3		3	1	1	6	15

Within 12 hours after infusion	Cisterna magna				Subarachnoid space		Vein	Total
	T.	P.	R.	A.	T.	P.	T.	
Highest temperature above 41°C	0	0		0	0	0	0	0
Highest rising degree over 2.0°C	0	0		0	0	0	0	0

Fig. 14 Cisternal Infusion with Air after Bilateral Electrocoagulation in the Anterior (45 days) and Posterior Hypothalamus (10 days)
Cisternal infusion with air 4.0-6.0 cc after pumping out liquor 2.0 cc.
♂53 3.5kg 27.2～27.8°C, 69.5～80%



with lesions involving both the anterior and posterior regions than in those limited solely to the anterior region (Figure 14).

This fever rising reaction is usually transitory, and only in extremely rare cases persists till the next day.

The cat having a hypothalamic lesion easily and highly raises the body temperature, especially when injected with typhoid vaccine as a pyrogen. This tendency is easy to recognize, when the results are compared among the animals which were examined at the same time and under the similar environmental condition, as shown in Figure 15 and 16. (In Table 8 and 9 are presented all the cases examined in different seasons, as a whole).

When a cat was injected with air, physiological salt water or Ringer's solution through the suboccipital route, the reaction is nearly similar after each injection, showing no essential difference among the three (Figure 17, 18).

Fig. 15 Intravenous Injection with Typhoid Vaccine (2.0 cc per kilogram body weight).
——— 1 : ♀60, Destruction of bilateral preoptic area with sublimate (4 days previously).
— — — 2 : ♂58, Mere trepanation (5 days previously).
- - - - - - 3 : ♀52, No operation.

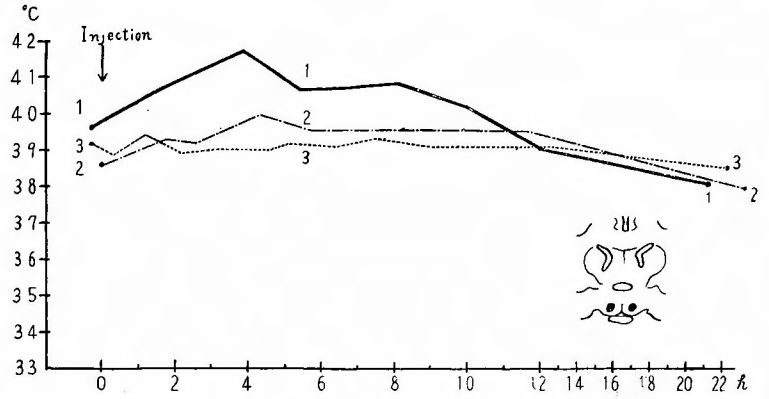


Fig. 16 Subarachnoidal Infusion with Physiologial Salt Water (1.5 cc).
——— 1 : ♀60, Destruction of bliateral preoptic area with sublimate (6 days previously).
— — — 2 : ♂58, Mere trepanation (7 days previously).

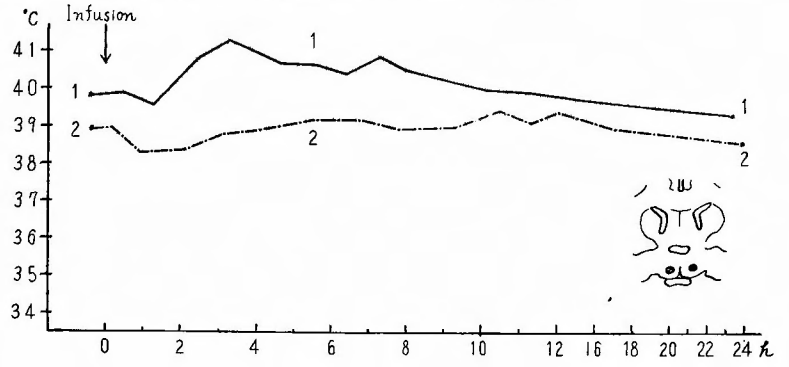


Fig. 17 o- - - - - - - o 1. In Cisterna Magna, Infusion with Physiological Salt Water.
× ——— × 2. In Cisterna Magna, Infusion with Air.
● - - - - - - ● 3. In Cisterna Magna, Infusion with *Ringer*'s Solution.
Previous lesion is in the preoptic area on one side.
♂94 3.0kg. 1. 10.5~11.4°C 2. 12.7~14.4°C 3. 10.5~12.2°C

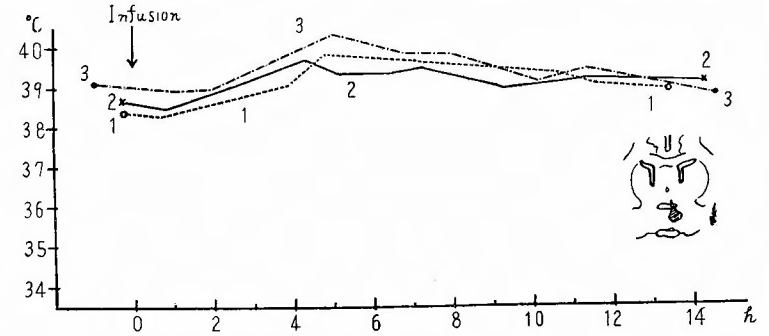
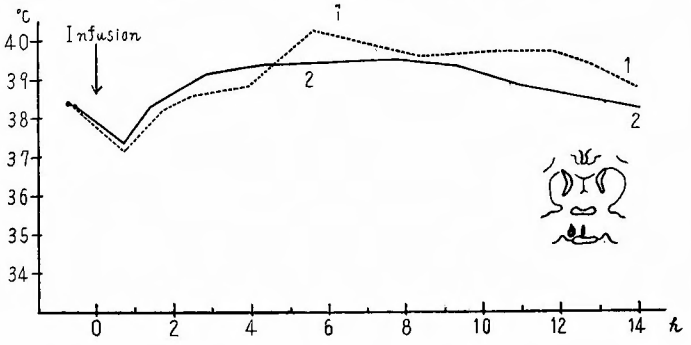


Fig. 18 ------- 1. In Cisterna Magna, Infusion with Physiological Salt Water.
——— 2. In Cistera Magna, Infusion with Air.
Previous lesion is in the preoptic area on one side.
♀95 2.5kg. 1. 10.5～12.2℃ 2. 10.5～11.4℃



The results were not influenced on by the time interval after electrocoagulation.

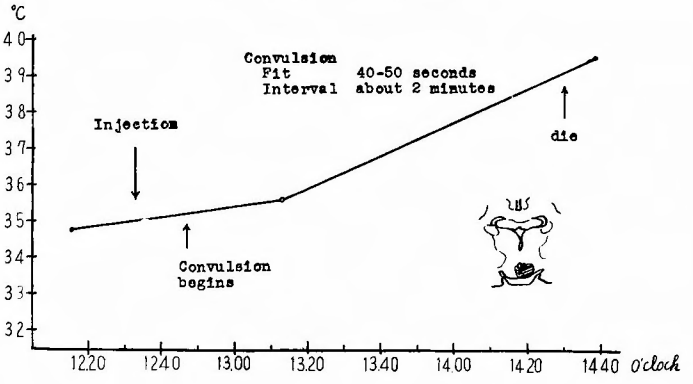
In the present experiments which were done more than several days after damage in the hypothalamus, type I hyperthermia was seen more frequently than in the two preceding experiments, and it is to be noticed that without use of typhoid vaccine I was able to produce the hyperthermia above 41°C or the rising degree of the body temperature above 2.0°C.

DISCUSSION

The present study was done to produce hyperthermia experimentally in the cat, and to investigate the mechanism of neurogenic hyperthermia. Experiments were done under the usual environmental temperature, in the freely movable state of the animal as much as possible, and taking much care to reduce the influences caused by anaesthesia, fixation and infection. The technical remarks made by RANSON were carefully referred to.

Autonomic nervous center is closely connected with extrapyamidal system including subthalamus etc., therefore the stimulation of this center influences the activity of skeletal muscles which constitute the great thermogenic system in the

Fig. 19 Cisternal Injection with Procaine-Penicillin (0.5 cc, 15×10^4 unit).
Previously electrocoagulated in the bilateral hypothalamus.
♂no. 3.0kg 25.6℃, 71%



body. Thus the muscular contraction raises the body temperature. For instance, if generalized convulsion is induced by penicillin injection into cisterna magna, the rectal temperature rises markedly as much as 3.0°C in one hour, and even in the postmortem the high temperature stands and does not easily fall down (Fig. 19).

In the present experiments the shivering noticed by RANSON et al. was not observed, only the panting was recognized, and probably for the same reason there were more cases of hyperthermia in RANSON's series than in mine.

At the beginning of the study, pure nicotine, which is an intense stimulating drug with some destructive action was injected into the hypothalamus. However, the animal fell into the severe shock state and exhausted the reserve energy for raising the body temperature.

The shock reaction was observed not only in the animals injected with nicotine into the brain, but also in those injected with the equal dosis of nicotine into other organs, hypoderm, muscle or vein. The shock of this kind occurs also as the result of an excessively damaging operation.

Considering that the body temperature is under the control of all organ systems of the body, it may be difficult to assume that hyperthermia is caused by a single mechanism, for instance loss of function of the heat dissipation center. Hyperthermia is realized necessarily by the concerted effects of the excitement of the thermoregulatory center together with the effective thermogenesis in the peripheral organ and systems acting in response to it. Thus, in order to produce hyperthermia in animals it is necessary to apply adequate stimulations without impairing the fever reserve power.

Whether the fever reaction following the local application of various chemicals or the electrocoagulation is to be attributed to the stimulating action or to the loss of function due to destruction is not determined.

RANSON showed that bilaterally symmetrical lesions in the anterior hypothalamus produced the abnormally high body temperature in the cat in the warm environment, but in the present experiments done in the usual environment, there was no definite difference in the results whether lesions were placed unilaterally or bilaterally, symmetrically or asymmetrically. This is the fact suggesting that some other factors than mere localisation may be involved in this problem.

In a case with type I hyperthermia above 42°C there were bilaterally large lesions though asymmetrically in the anterior hypothalamus leaving the posterior hypothalamus intact. This finding is in accord with RANSON's assertion. But in another case with the similar lesions and experimented under the similar condition, the highest body temperature was only around 40°C, though it belonged to type I.

These facts suggest that mere destruction of anterior hypothalamic region on both sides does not always result in marked hyperthermia. Similar trend is noticed in the secondary fever experiments, too.

The present experimental results with electrocoagulation are, however, not much different from the results by RANSON et al. Namely, hyperthermia of above 40°C in his experiments occurred in eight of twenty-nine in the monkey, and seven of

eleven in the cat. In his experiments, the animals after operation were confined in a hammock and kept in an incubator regulated at or a little above 28°C, i e. in the higher environmental temperature than in the present experiment It was shown in his experiments, that induced hyperthermia is of lower degree in the cat than in the monkey under the similar condition. In the monkey large hypothalamic lesions brought about seldom shock, and frequently a sharp rise in the body temperature, at times even fatal hyperthermia, as seen in patients of severe head injury. In the man hyperthermia seems to occur more easily than in the animals.

There are many reports in which animals with various brain injuries and diseases revealed the abnormality of the body temperature regulation, as demonstrated by fever curve in the normal environmental temperature, gas metabolism with oxygen and carbonic acid, and fever reaction in the warm and cold environments.

Using the cats with a hypothalamic lesion, McCrum et al. reported on what is called morphine hyperthermia (Oglesby, 1870), in which hyperthermia was produced by intravenous injection with morphine.

Suggested by this method, I attempted to produce hyperthermia by the cisternal injection with air, physiologic saline solution or typhoid vaccine.

There are also many reports on the changes in the body temperature after injecting air or others into subarachnoid space and also on the changes due to fluctuations of liquor pressure.

Takamura in our clinic pointed out that hyperthermia after iodized-oil-ventriculography was most frequently seen in the cases with obstruction of aquaeductus mesencephali and or dilatation of the third ventricle, and Hoshino succeeded in preventing hyperthermia after iodized-oil-ventriculography by continuous ventricle drainage.

In the present experimental study, using cats with hypothalamic lesions, I was able to produce the abnormally high body temperature by the injection with air, physiological saline solution or Ringer's solution in the liquor space and recognized that the animal having such hypothalamic lesions tended to show the higher rising degree of fever, when injected intravenously and in the liquor space with typhoid vaccine.

In the primary fever experiments the larger lesions tended to produce the higher rise in the body temperature, as far as the animals did not fall into shock, while in the secondary stimulating experiments small but widely scattered lesions in various parts of the hypothalamus seemed to cause the higher fever rise. The same may be true in the warmed environment.

There is disagreement of opinions as to Ranson's hypothesis that the heat dissipation center lies in the anterior hypothalamus (preoptic area), while the heat production and conservation center in the posterior hypothalamus. Hess, Kurozu and Abe etc. presented different opinions respectively on the regulation center of the body temperature from their view points. During the past few years, McCrum, Sherwood, Massopust & Buchanan have objected to Ranson's hypothesis.

On the other hand Mondori in our clinic reported that in the histological study of the hypothalamus of the patients with a hypophyseal tumor who died of

postoperative hyperthermia, remarkable changes probably due to tumor compression were found in the anterior hypothalamus including the wall and the base of the third ventricle and its adjacent area from the preoptic area to the tuber cinereum, but he did not definitely conclude which nucleus or which area would be responsible for hyperthermia, because the evaluation of histological changes in relation to hyperthermia should be very careful. In the present experiments too, we could neither define hypothalamic nuclei and areas responsible for hyperthermia, nor obtain a positive evidence that such a limited center or centers certainly lie in the hypothalamus.

It may be sure that the hypothalamus is important for thermoregulation but it is difficult to conclude definitely that the hypothalamus is the only area concerned with thermoregulation in the brain.

SUMMARY AND CONCLUSION

The experiments were performed in one hundred and twenty adult, healthy cats. In these cats injection with various chemicals or electrocoagulation in the diencephalon and mesencephalon, mainly in the hypothalamus, was done and after some days secondary stimulating procedures were applied.

The following results were obtained.

1. The normal rectal temperature averaged from the data in seventy six healthy cats was 39.0 ± 0.1°C.

2. The rectal temperature falls by fixation on a table, anaesthesia and operation.

3. Hyperthermia of above 41°C in rectal temperature and of over 2.0°C in rising degree does not usually take place by injection of chemicals or electrocoagulation in the brain, under the usual room temperature. Even if it does, it lasts only for a short time.

Thus, it is difficult in the cat to imitate the hyperthermia which is observed in the normal man after severe brain injury. But if general convulsion occurs, body temperature rises steeply.

4. In the mechanisms of inducing hyperthermia, not only the stimulation or destruction of the thermoregulatory center but also the species of animals, the individual difference and the environmental condition seem to play important parts.

5. For producing high body temperature the stimulating or destructive procedures should not be too great in order to avoid the break down of the thermogenic reserve power. If light or moderate stimulations, such as injection in the liquor space with typhoid vaccine, air, physiological salt water or RINGER's solution or intravenous injection with typhoid vaccine, are applied secondarily after recovery from the damage in the hypothalamus, then hyperthermia takes place rather easily, whereas it does not in cases of acute severe lesions in the hypothalamus of the animal previously untreated. This fact suggests that a patient having the hypothalmus previously damaged by a hypophysial tumor or the like, may easily show the higher rise in the body temperature than in the normal man, if he is secondarily affected by infectious diseases or sustains operative or traumatic head injuries.

6. In the present study we could not decide the definite localisation of the thermoregulatory center or of the area to be regarded as the probable source of hyperthermia. It was our impression that not the localisation but the severity of a lesion would be more important for the occurrence of hyperthermia.

Surely the hypothalamus plays an important rôle in the thermal regulation but the other parts of the brain do not seem to be unconcerned with it. Should we not attach to great importance merely to the hypothalamus in the mechanism of the themoregulation?

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和文抄録

中枢神経性過高熱の実験的研究

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猫120匹を用い，視床下部を主とする間脳脳幹部に各種薬液（ニコチン，昇汞，其他）の注入及び電気凝固を行い，急性期の発熱反応を検し，次でこの破壊巣を有する猫に時日を経て更に他の各種刺戟（チフスワクチン，生理的食塩水，リンゲル液，空気等の大槽内注入，チフスワクチン，生理的食塩水の蜘網膜下腔注入及び静脈内注入等，其他）を加えた場合の体温反応を観察し猫に於ける過高熱の実験的研究を種々の面より検討を加えた．

1. 猫76匹の平均直腸温は39.0±0.1℃である．
2. 固定，麻酔及び手術により他の動物の場合と同様，猫に於ても直腸温は低下する．
3. 猫に於て常温環境下で直腸温41℃以上，又は上昇度2.0℃以上を得んとするには単なる脳内に於ける生液注入や電気凝固のみでは難しく特に人体臨床例の如き持続した過高熱を得ることは極めて困難である．即ち健康人の頭部外傷時に見られる過高熱を猫に於て模倣することは難し

い．但し全身麻痺のある場合には体温は著しく上昇し得る．

4. 体温の変動に対しては単なる体温調節中枢への刺戟条件のみではなく動物種別，個体差及び環境条件をも充分考慮すべきである．
5. 体温の上昇を求めるには動物の発熱への予備力を損ぜぬ様に刺戟を加うべきである．直接視床下部に大なる刺戟侵襲を加えるよりも視床下部に予め傷害を与へ体力の回復をまつて髄液腔内へのチフスワクチン，空気，生理的食塩水，リンゲル液等の注入，静脈内へのチフスワクチン注入の如き比較的簡易なる刺戟を与えた方がより発熱し易い．このことは人間に於て脳下垂体腫瘍其他によつて視床下部が予め傷害されている場合には，伝染病への罹患とか脳手術とかによつて普通人よりも高い発熱を来し易いであろうことを示唆する．
6. 本実験では視床下部内を更に細部に分つて部位的に特に過高熱を来し易い部と然らざる部とを認めることは出来なかつた．寧ろ巣の大小の方に重要性を認めた．又視床下部が体温調節に重要な役割を果すものとは考えられたが，然し脳の他の部分も無関係ではなく現在迄の視床下部のみに重要性を求める行き方には考慮を要するものと思われた．